suspension is then spray dried to form a freely flowable powder which exhibits controlled-release properties when directly compressed.

REMARKS

Reconsideration and allowance of the subject application are respectfully requested.

Claims 1, 2, 4-9, 11-13 and 15-25 are pending in the application.

Claims 1, 2, 13 and 19-24 have been amended to clarify that the spray-dried particles are free flowing and that the formulation has controlled-release properties when compressed into tablets. The free flowing particle form does not exhibit controlled-release properties. Basis for this amendment can be found in the present specification including at page 11, lines 16-28, page 25, lines 5-27, and page 28, line 4. No new matter has been added.

An explanation of the amendment is attached herewith.

Basis for the amendment to claims 4-7 regarding the language "by weight" can be found in the present specification including at page 28, line 30. No new matter has been added.

The rejection of claims 1, 2, 4-9, 11-13, 15-25 under 35 U.S.C. § 112, second paragraph, is obviated in part by the amendment to the claims shown above and traversed in part.

The part of the Section 112 rejection regarding the language "wherein in case of cellulose materials these cellulose materials are cellulose derivatives" is obviated by the amendment to cancel this language from claims 1, 13, 19, 20, 23 and 24 as set forth above.

The part of the Section 112 rejection regarding the percentages in claims 2, 4-9, 11-13 and 15-25 is obviated by the amendment to clarify that the percentage is based on weight, as set forth above.

The part of the Section 112 rejection regarding the terms "coherent," incoherent" and "a matrix-material-containing compound" is respectfully traversed for the following reasons.

The term "compound" used in the present invention does not relate to a chemical compound in the sense of typical chemical patent applications or texts. In Pharmaceutical

Technology terminolgy "a compound" is a particle which is composed of several excipients (e.g. lactose and polymer) and used for a certain purpose, such as an intermediate product in a process to produce a dosage form like a tablet or implant. See page 1, paragraphs 1 and 2, which describes the use of the term compound. Another more precise term is "excipient compound". However, usually the scientific pharmaceutical literature refers merely to the term "compound" instead of excipient compound. As an example, a copy of a technical sheet of a German food company, Meggle GmbH, is enclosed which clearly shows the use of the term "compound" as explained above.

- If the "compound" contains for example an excipient which is able to form a matrix network (e.g. a polymer) besides other excipients (e.g. lactose), such a compound is referred to as a **matrix material-excipient compound**.
- If the "compound" contains for example an excipient which is able to form a matrix network (e.g. a polymer), no other excipients and a drug (active substance), such a compound is referred to as a **matrix material-active substance compound**.
- If the "compound" contains for example one excipient which is able to form a matrix network (e.g. a polymer), also other excipients (e.g. lactose) and a drug (active substance), such a compound is referred to as a **matrix material-excipient-active substance compound**.

In the present description, the term matrix material-containing compound is sometimes used instead of material matrix-excipient compound.

The terms "coherent" and "incoherent" are terms frequently used in Pharmaceutical Technology. "Incoherent" means that several subjects are not in direct connection with each other, i.e. they do not form one continuous phase. For example, the oil in an oil-in-water emulsion is the incoherent phase. The single oil droplets are not in touch and separated from each other. "Coherent" means that several subjects are in direct connection with each other, i.e. they form one continuous phase. The water phase in an oil-in-water emulsion is the coherent phase. Thus, the terms "coherent" and "incoherent" are well defined in Pharmaceutical Technology.

The present invention provides spray-dried particles, which can be easily compacted into a larger matrix, pellets or tablets as desired because of their unique flow characteristics. See page 11, lines 16-28 and page 25, lines 5-27, of the present specification. The spray-dried particles have an incoherent matrix material phase and a coherent active substance and/or excipient phase - in other words, distinct particles of the

polymer matrix are embedded in the excipient or active substance phase as shown in the Figures attached to the present specification. The spray dried particles do not exhibit controlled-release properties until compacted into a larger matrix, pellet or tablet form.

For these reasons, Applicant submits that the claimed invention fully complies with Section 112. Accordingly, withdrawal of the Section 112 rejection is respectfully requested.

The rejection of claims 1, 2, 4-9, 11-13, 17, 19 and 20 under 35 U.S.C. § 102(b) over McClelland is respectfully traversed. Claims 1, 2, 4-9, 11-13, 17, 19 and 20 are not anticipated by McClelland for the following reasons.

Applicant notes that the Examiner agrees that McClelland does not teach forming spray dried particles according to the present invention. Applicant submits that the presently claimed spray dried particles are novel over the particles of McClelland for the following reasons.

McClelland discloses spherical multiparticulates consisting of a charged resin, other excipients and optionally a medicament. While both McClelland's particles and the present formulation may contain similar groups of excipients and they both possess a spherical form, this does not necessarily imply that the products themselves are identical and have identical functional properties.

The particles of McClelland are produced by a conventional wet granulation process, the speciality being that incorporation of the charged resin makes the spheronisation process efficient and simple (page 1, lines 11-12 of McClellan). McClelland claims this special process of simple wet granulation in his claim 1 which probably only works with a limited number of charged resins, as recited in his claim 3.

The present invention, however, covers a wide range of polymers and also lipids as matrix material and – in contrast to McClelland - is not limited to resins being charged and simultaneously limited in number.

A wet granulation process, such as McClelland results in the formation of a coherent matrix material phase and an incoherent excipient and active substance phase. Contrary to this, the spray drying process according to the present invention results surprisingly in the formation of an incoherent matrix material phase and a coherent excipient and active substance phase. Thus, the claimed formulation has a very different structure than the particles of McClelland and is therefore patentable over McClelland.

In general, the properties of a product are determined by the product structure. The resins of McClelland provide the required plasticity to the extrusion mass for extrusion

or spheronization. The resins are used as a substitute for cellulose (see page 2, lines 29-31). However, such a plasticity requirement is not a required property of the present invention. No high shear granulation or extrudation is required in the present invention, only spray drying.

The Examiner states that the particles of McClelland "have unexpectedly good flow properties". However, in the whole patent application of McClelland there is no single statement about the flow properties of the multiparticulate product. Therefore, the Examiner's statement is not supported by any facts and should be withdrawn.

Applicant wonders whether the Examiner is referring to the good flow (extrusion) properties of the mass used for preparing the multiparticulates. This good flowability is due to the charged resins resulting in plasticity of the mass. However, the rheological flow of the intermediate product extrusion mass has nothing to do with the flow of the final, dry powdered product of McClelland.

In contrast to the Examiner's allegations, the multiparticulate powdered product of McClelland does not have free flowing properties, nor does it have good direct compressibility. In contrast, the particles of the present invention have good flowability (free flowable) in combination with good direct compressibility.

For these reasons, McClelland cannot anticipate the claimed invention. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1, 2, 5-9, 11, 12 and 17-20 under 35 U.S.C. § 102(e) over Sparks is respectfully traversed. Claims 1, 2, 5-9, 11, 12 and 17-20 are not anticipated by Sparks for the following reasons.

Sparks describes a controlled release tablet consisting of a core surrounded by a release controlling membrane, which provides a certain prolonged release profile.

In contrast, the present invention claims:

1. a particulate "compound" with special flow (free-flowing) and direct compressibility properties due to the special structure with respect to coherent and incoherent phases (claim 1) and

2. use of this particulate "compound" for compression into larger units (claims 12, 17 and 18), e.g. a controlled release tablet (see Fig. 2 in the present application).

Sparks does not describe the particulate compound of the present invention.

The only similarity between Sparks and present invention is that they both describes a controlled release tablet which is able to provide a prolonged release. However, the present invention achieves controlled release by a very different mechanism than Sparks. The controlled release tablet according to Sparks consists of a core surrounded by a membrane. In contrast, the present invention describes tablets requiring only a matrix material, active substance and/or excipient in order to provide prolonged release. The spray dried powder according to the present invention can be used to form a controlled-release by direct compression, without requiring the use of a membrane.

The tablet of Sparks contains a core which is rapidly soluble, preferentially 90% in less than 30 minutes (column 3, lines 61-64). The matrix of the present invention – corresponding to the core – does not dissolve fast and can retain its structure for hours. This difference in functionality of the inner parts of the two products is caused by a difference in structure.

The Examiner states that the characteristic membrane-free is not within the pending claims. The presence or absence of a membane is irrelevant. Sparks simply does not anticipate or even suggest spray dried particles according to the present invention which are capable of providing a controlled-release tablet by direct compression, without requiring the use of a membrane.

The Examiner states that the Sparks composition contains all instant components and has the same functional characteristics. However, same components (e.g. polymer, excipient, drug) and identical property of controlled release does not allow one to conclude automatically that the system structure is identical. Sparks does not teach or suggest the coherent and incoherent structure of the claimed particles.

For these reasons, Sparks cannot anticipate the claimed invention. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1, 2, 4-9, 11, 12, and 17-20 under 35 U.S.C. § 102(e) over Motta is respectfully traversed. Claims 1, 2, 4-9, 11, 12, and 17-20 are not anticipated by Motta for the following reasons.

Motta describes the production of a controlled release tablet. However, Motta does not disclose the particle "compound" of the present invention. The presently claimed "compounds" are powdered intermediate mix products for tablet production.

In contrast, Motta describes a process to produce a controlled release tablet using a traditional direct compression mixture containing simple powdered excipients e.g. lactose or a polymer and drug. Each particle is composed of only one chemical substance, e.g. pure lactose particles.

The present invention compresses compound particles, each particle being composed of a minimum of 2 chemical substances, e.g. an excipient compound: lactose, polymer (or lipid) an excipient-drug compound: lactose, polymer or lipid and drug.

The compound particles according to the present invention enclose polymer (or lipid) particles in a continuous matrix of excipient, e.g. lactose (Fig. 2). Compression of these compound particles to a larger unit will create a coherent phase of excipient in which polymer (or lipid) particles are separately embedded (i.e. because the particles are separated, they represent the incoherent phase). It is characteristic for the large units of the present invention that the excipient phase is always coherent. In other words, the polymer or lipid particles are not in touch with each other (incoherent) and single particles, separated.

The tablet produced by Motta does not comprise this structure. Moreover, Motta does not disclose any detailed information about the internal structure of his tablets. Fig. 6 of Motta does not allow detailed conclusions.

For these reasons, Motta cannot anticipate the claimed invention. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1, 2, 4-9, 11-13, 15-20 and 23-25 under 35 U.S.C. § 102(e) as being anticipated by Norling is respectfully traversed. The rejection of claims 1, 2, 4-9, 11-13, and 15-25 under 35 U.S.C. § 103 over Norling is respectfully traversed. Applicant respectfully submits that claims 1, 2, 4-9, 11-13, 15-20 and 23-25 are not anticipated by nor obvious over Norling for the following reasons.

Norling describes a controlled release unit in the form of a pellet, but he does not describe an compound particle for direct compression as the present invention. Just because Norling teaches controlled release does not mean that the structure of Norling's pellets is identical to the claimed invention. Something can have an identical property (e.g. identical release pattern) but being completely different in structure. For example, identical release patterns can be obtained from a reservoir patch and a clever designed laminated patch, but the structure of the systems are completely different.

Norling does not produce spray-dried pellets as stated by the Examiner on page 6 of the Office Action. Norling is employing spray-drying for producing the core of his pellets (column 3, lines 46-49, example 1A, 1B, 1C), which core is then coated in a fluidized bed apparatus (example 4). The cores consist mainly of an inorganic material such as calcium carbonate. The core can also contain a drug (example 3). The claims by Norling clearly specify that the final release formulation consists of "coated cores" (first sentence in claim 1). Thus, Norling discloses a very different structure than the large controlled release units of the present invention, which are produced by direct compression of the claimed compound particles (Figure 3).

For these reasons, Norling cannot anticipate the claimed invention. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

In view of all of the objections and rejections of record having been addressed, it is believed that the present application is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 62-659

In re patent application of Muller
Serial No. 09/319,541
Filed: 8/19/99

Group Art Unit: 1616
Examiner: Shahnam Sharareh

For: PREPARATION IN FORM OF A MATRIX-AUXILIARY AGENT COMPOUND CONTAINING OPTIONALLY AN ACTIVE SUBSTANCE

May 7, 2001

EXPLANATION OF AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The claims have been amended as shown by insertions and [deletions].

IN THE CLAIMS:

1. (Amended) [Prolonged-release formulation] Formulation in the form of a matrix material-containing compound comprising:

an excipient phase comprising at least one excipient;

an active substance phase comprising at least one active substance; and

a matrix material phase comprising at least one polymer or lipid, [wherein in case of cellulose materials these cellulose materials are cellulose derivatives and] wherein the formulation is in the form of a freely flowable powder of spray-dried particles in which the matrix material phase is incoherent and the excipient ~~and active substance phases are coherent, and the formulation provides~~ controlled-release properties when directly compressed.

2. (Amended) [Prolonged-release formulation] Formulation in the form of a matrix material-containing compound comprising:

an excipient phase comprising at least one excipient;

an active substance phase comprising at least one active substance; and

a matrix material phase comprising at least one polymer or lipid, wherein in case of cellulose the portion of the matrix material phase of the

formulation is 70 to 98% by weight, and wherein the formulation is in the form of a freely flowable powder of spray-dried particles such that the matrix material phase is incoherent and the excipient and active substance phases of the formulation are coherent, and the formulation provides controlled-release properties when directly compressed.

4. (Amended) Formulation according to any one of claims 1, 2 and 19-22, wherein the content of the matrix material phase of the formulation is 1 to 98 % by weight.

5. (Amended) Formulation according to any one of claims 1, 2 and 19-22, wherein the content of the matrix material phase of the formulation is 10 to 95 % by weight.

6. (Amended) Formulation according to any one of claims 1, 2 and 19-22, wherein the content of the matrix material phase of the formulation is more than 15 % and not more than 90 % by weight.

7. (Amended) Formulation according to any one of claims 1, 2 and 19-22, wherein the content of the matrix material phase of the formulation is 40 to 70 % by weight.

8. (Amended) Formulation according to any one of claims 1, 2 and 19-22, wherein the matrix material phase comprises at least one selected from the group consisting of polyacrylate, polymethacrylate, naturally occurring, semi-synthetic and synthetic triglycerides or mixtures thereof, mono- and diglycerides by themselves or in a mixture with one another or with triglycerides, naturally occurring and synthetic waxes, fatty alcohols, including their esters and ethers, and lipid peptides[, in particular synthetic mono-, di- and triglycerides as individual substances or in a mixture, specifically hydrogenated fat, glycerol tri-fatty acid esters, specifically glycerol trilaurate, -myristate, - palmitate, -stearate and -behenate, and waxes, specifically cetyl palmitate and cera alba (bleached wax, German Pharmacopeia, 9th edition) or beeswax]. Deleted

13. (Amended) Process for the preparation of a [prolonged-release] formulation in the form of a matrix material-containing compound comprising:

an excipient phase comprising at least one excipient;

an active substance phase comprising at least one active substance; and

a matrix material phase comprising at least one polymer or lipid, [wherein in case of cellulose materials these cellulose materials are cellulose derivatives, and] wherein the formulation is in the form of spray-dried particles in which the matrix material is incoherent and the excipient and active substance phases are coherent, wherein the phases of the formulation are suspended or suspended and dissolved together in a liquid to form a suspension, the matrix material phase being insoluble in the liquid, and this suspension is then spray dried to form a freely flowable powder which provides controlled-release properties when directly compressed.

19. (Amended) [Prolonged-release formulation] Formulation in the form of a matrix material-containing compound comprising:

an excipient phase comprising at least one excipient; and

a matrix material phase comprising at least one polymer or lipid, [wherein in case of cellulose materials these cellulose materials are cellulose derivatives, and] wherein the formulation is in the form of a freely flowable powder of spray-dried particles in which the matrix material phase is incoherent and the excipient phase is coherent, and the formulation provides controlled-release properties when directly compressed.

20. (Amended) [Prolonged-release formulation] Formulation in the form of a matrix material-containing compound comprising:

an active substance phase comprising at least one active substance; and

a matrix material phase comprising at least one polymer or lipid, [wherein in case of cellulose materials these cellulose materials are cellulose derivatives, and] wherein the formulation is in the form of a freely flowable powder of spray-dried particles in which the matrix material phase is incoherent and the active substance phase is coherent, and the formulation provides controlled-release properties when directly compressed.

21. (Amended) [Prolonged-release formulation] Formulation in the form of a matrix material-containing compound comprising:

an excipient phase comprising at least one excipient; and

a matrix material phase comprising at least one polymer or lipid, wherein [in case of] when said polymer comprises cellulose the portion of the matrix material phase of the formulation is 70 to 98% by weight, and wherein the formulation is in the form of a freely flowable powder of spray-dried particles such that the matrix material phase is incoherent and the excipient phase of the formulation is coherent, and the formulation provides controlled-release properties when directly compressed.

22. (Amended) [Prolonged-release formulation] Formulation in the form of a matrix material-containing compound comprising:

an active substance phase comprising at least one active substance; and

a matrix material phase comprising at least one polymer or lipid, wherein in case of cellulose the portion of the matrix material phase of the formulation is 70 to 98% by weight, and wherein the formulation is in the form of a freely flowable powder of spray-dried particles such that the matrix material phase is incoherent and the active substance phase of the formulation is coherent, and the formulation provides controlled-release properties when directly compressed.

23. (Amended) Process for the preparation of a [prolonged-release] formulation in the form of a matrix material-containing compound comprising:

an excipient phase comprising at least one excipient; and

a matrix material phase comprising at least one polymer or lipid, [wherein in case of cellulose materials these cellulose materials are cellulose derivatives, and] wherein the formulation is in the form of spray-dried particles in which the matrix material is incoherent and the excipient phase is coherent, wherein the phases of the formulation are suspended or suspended and dissolved together in a liquid to form a suspension, the matrix material phase being insoluble in the liquid, and this suspension is then spray dried to form a freely flowable powder which exhibits controlled-release properties when directly compressed.

24. (Amended) Process for the preparation of a [prolonged-release] formulation in the form of a matrix material-containing compound comprising:

an active substance phase comprising at least one active substance; and

a matrix material phase comprising at least one polymer or lipid, [wherein in case of cellulose materials these cellulose materials are cellulose derivatives, and] wherein the formulation is in the form of spray-dried particles in which the matrix material is incoherent and the active substance phase is coherent, wherein the phases of the formulation are suspended or suspended and dissolved together in a liquid to form a suspension, the matrix material phase being insoluble in the liquid, and this suspension is then spray dried to form a freely flowable powder which exhibits controlled-release properties when directly compressed.

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